REMARKS/ARGUMENTS

Claim amendments

Claims 121-123 have been amended to recite "growth factor stimulated". Support for the claims as amended is present implicitly in the claims as originally presented (given the roles of growth factors and endothelial cells in "angiogenesis in a tissue" as recited in the claims) and at least on page 16, lines 25-28 of the instant application. No change in the scope of subject matter encompassed by the claims is believed to have occurred and thus no narrowing of the claims has occurred.

Claim 151 has been amended to correct a typographical error.

Claims 152-157 have been canceled without prejudice for re-presentation in a subsequent continuing application. The cancellation should not be viewed as an admission of the correctness of the Office's position or as an abandonment of the subject matter. To the contrary, the cancellation is made for reasons related to business considerations and the fact that the subject matter of canceled claims 152-157 remains fully within the scope of claims 121 and 123, from which claims 152-157 previously depended.

No new matter has been presented, and entry of the above amendments is respectfully requested.

Telephonic interview of November 24, 2003

Applicant thanks Examiner Susan Unger for the courtesy of a telephonic interview on November 24, 2003 with Applicant's representatives Karen Dow and Kawai Lau. During the interview, the above presented claim amendments were discussed, and Applicant appreciates the Examiner's indication that the amendments appeared to resolve all outstanding issues under 35 U.S.C. § 112, first paragraph.

The interview continued with a discussion of the cited references and the rejections under 35 U.S.C. § 102 and 103 based on US Patent 5,922,676 (Pasqualini) and USP 5,922,676 in view of WO 95/14714 (Ruoslahti et al.), Thorpe, Guo et al. and Scott et al. Examiner indicated that based on her view that superfibronectin (sFN) is a multimer of fibronectin (FN), the rejections of

record were adequately supported in the absence of indications that sFN and FN were functionally different. Applicant's representatives agreed to investigate whether relevant evidence of functional differences between sFN and FN was available, and if so, to present it in the next response.

Rejection of Claims 121-123 under 35 USC § 112, first paragraph

Claims 121-123 were rejected under 35 USC § 112, first paragraph, allegedly due to the addition of new matter not described in the Specification. (See Paragraph 4 on page 2 of the Office Action.)

As noted above, the claims have been amended to expressly recite "growth factor stimulated" as implicitly present in the claims as filed and as supported by the instant specification. Applicant respectfully submits that this is believed to obviate the basis of the rejection. Accordingly, withdrawal of the instant rejection, including the inclusion of claims 124-151 which depend from claims 121-123, is respectfully requested.

Claims 152-157 were rejected under 35 U.S.C. § 112, first paragraph, allegedly due to a lack of support for terms used in the claims. Without acquiescing to the instant rejection as noted above, claims 152-157 have been canceled without prejudice and with the understanding that the subject matter encompassed by claims 152-157 remain fully within the scope of the claims from which claims 152-157 depended. Accordingly, withdrawal of the instant rejection is respectfully requested.

Claim 151 was rejected under 35 U.S.C. § 112, first paragraph, apparently due to the presence of a typographical error in the claim. As noted above, the typographical error has been corrected, and so withdrawal of the instant rejection is respectfully requested.

Rejection under 35 USC 102(e)

Claims 121-131, 135-144, 147, and 149-157 were rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 5,922,676 (Pasqualini et al.) as evidenced by PCT

Application WO 95/14714 (Ruoslahti) and Pytela et al., Cell 1985, 40:191-198. Applicant respectfully traverses the rejection as having failed to present a *prima facie* case of anticipation.

The instant rejection appears to be based upon the view that the cited reference by Pasqualini et al. (USP '676) discloses

> "the same method steps as claimed in the instant invention, that is, administering an antagonist, which binds alpha 5 beta 1 integrin (which is expected to interfere with the specific binding of endogenous ligand to alpha 5 beta 1 integrin for the reasons of record) to the same population ... thus the claimed method is anticipated because the method will **inherently** lead to reducing or inhibiting angiogenesis. See Ex parte Novitski...." (page 8, first paragraph, of the Office Action mailed October 14, 2003, emphasis added)

The above view, along with the reliance upon "inherency" and *Novitski*, is reiterated on page 10 of the Office Action with respect to the language of "induces growth factor stimulated endothelial cell apoptosis" as found in claims 121-123.

Applicant thus understands from the above language, and from the telephonic interview of November 24, 2003, that the instant rejection is based upon an allegation that superfibronectin (sFN) has an inherent (rather than disclosed) property of acting as an antagonist of $\alpha 5\beta 1$ integrin to induce "growth factor stimulated endothelial cell apoptosis". This is consistent with the fact that none of the cited references (Pasqualini et al. (USP '676), WO 95/14714 (Ruoslahti) or Pytela et al) describes or suggests that sFN has such an antagonistic activity.

This Examiner's reliance on an inherent property of sFN appears to be based upon the Examiner's assertions in the instant rejection that fibronectin is the only ligand for $\alpha 5\beta 1$ integrin and that sFN is but a multimeric form of fibronectin. Consequently, the Examiner concludes that Pasqualini et al.'s use of sFN would interfere sufficiently with the binding of fibronectin to $\alpha 5\beta 1$ integrin to anticipate the instant claims based upon inherency. Applicant respectfully points out, however, that even if Pasqualini et al. (USP '676) supports the position that sFN binds as a ligand to $\alpha 5\beta 1$ integrin, mere binding is not sufficient to establish that sFN is an antagonist that "induces growth factor stimulated endothelial cell apoptosis" and to meet the burden of a *prima facie* case of anticipation based upon inherency. There is simply no evidence that apoptosis of

growth factor stimulated endothelial cells is a necessary consequence of sFN binding to $\alpha 5\beta 1$. The standard for inherent anticipation requires that a characteristic or result be "a necessary consequence" of that which is disclosed.[1] Moreover, "inherency, like anticipation itself, requires a determination of the meaning" of references applied against the claims.[2]

As the Examiner is aware, Pasqualini et al. (USP '676) fail to disclose or suggest that treatment with sFN induces apoptosis of any cell. Additionally, Pasqualini et al. (Nat Med. 2(11):1197-1203, 1996, of record) state that "[s]uperfibronectin appears to suppress metastasis, rather than affect growth of established tumors" (see page 1200, right column, first sentence). Thus, although tumor angiogenesis is required for established tumors to grow, Pasqualini et al. (1996) does not teach or suggest that sFN effects angiogenesis. This is consistent with the disclosure in Pasqualini et al. (USP '676), which describes how KRIB osteocarcinoma cells and C8161 melanoma cells were inhibited from spreading and migrating without any indication of apoptosis in these cells (see columns 24-26, Example VIII). This is also consistent with the discussion in Yi et al. (Proc. Natl. Acad. Sci., USA, 98(2):620-624, 2001, of record), which cites Pasqualini et al. (1996) in stating that "sFN had little or no effect on the growth of the primary tumors" (see Yi et al., page 621, left column, second full paragraph).

Furthermore, Applicant respectfully reminds the Examiner that sFN is described as having greatly enhanced cell adhesive properties relative to fibronectin (see Morla et al., 1994, of record, and also Pasqualini et al. (USP '676) at column 4, lines 19-22) and ameliorates metastasis "by paralyzing adherence and/or migration mechanisms of cells" (see Pasqualini et al. (USP '676) at column 3, lines 63-66). Therefore, sFN does not function identically to fibronectin as asserted in the instant rejection.

This sFN activity is also the very **opposite** of an $\alpha 5\beta 1$ integrin antagonist's activity as described by Kim et al. (Am. J. Path., 156(4):1345-1362, 2000, in the IDS filed herewith), where antagonists **block** cell adhesion and angiogenesis (see pages 1352-1353, including Figure 4).

The same effects by an integrin antagonist in an analogous context are discussed by Kumar et al. (J. Pharmacol. Exp. Therap., 283(2):843-853, 1995, of record), who describe

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[1] See for example, *Mehl/Biophil Int'l. Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) and *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

[2] See *Schering Corp. v. Geneva Pharmaceuticals*, 339 F.3d 1373, 1377, 67 U.S.P.Q.2d 1664, 1667 (Fed. Cir. 2003).

echistatin (a 49 amino acid peptide) as a potent antagonist of αvβ3 integrin mediated cell adhesion to a vitronectin matrix (see abstract and pages 850-851, bridging paragraph). Additionally, Kumar et al. further point out that

> "It is worth noting an important biochemical distinction between vitronectin and echistatin. Vitronectin exists as a multimer containing between 12 and 15 moieties per multimer [citation omitted]. There is also evidence that multimeric vitronectin is also present in extracellular matrices *in vivo*. In contrast, echistatin used in these studies is a monomer as determined by mass spectral analysis (data not shown). The multimeric nature of vitronectin results in higher nonspecific binding in solid-phase receptor binding assays. On the other hand, echistatin shows very little non-specific binding in these assays, and binds to αvβ3 with high affinity..." (see pages 851-852, bridging paragraph).

Applicant respectfully points out that the relationship between αvβ3's antagonist echistatin vis-à-vis vitronectin may be analogous to the relationship between α5β1's antagonist vis-à-vis fibronectin or sFN in that the integrin antagonist of each pair may display very little non-specific binding while the multimeric vitronectin or sFN molecules of each pair may display higher levels of non-specific binding. If so, the effects of sFN described by Pasqualini et al. (USP '676) alleged to support the instant rejection may simply be due to non-specific binding by sFN rather than sFN activity as an α5β1 antagonist.

Given the above, and in response to the statements of the instant rejection on pages 5-6 (bridging paragraph) of the Office Action mailed October 14, 2003, Applicant respectfully submits that the subject matter of the instant claims are distinct from the use of sFN described by Pasqualini et al. (USP '676). Clearly, Pasqualini et al. (USP '676) do not teach the use of sFN as an α5β1 integrin antagonist, and Applicant submits that the Examiner has not met the burden of demonstrating why sFN is inherently such an antagonist. Accordingly, Applicant has no burden to provide further evidence comparing the claimed methods to the disclosure of Pasqualini et al. (USP '676) as required by the instant rejection.

With respect to the allegation on pages 6-7 (bridging paragraph) of the Office Action mailed October 14, 2003 that Pasqualini et al. (USP '676) disclose the use of sFN to cause "regression of established primary tumors *in vivo*" in Example VII (columns 21-23), Applicant

respectfully, but strongly, disagrees. While Example VII describes the use of sFN as resulting in the regression of two established tumor types (Bend tumor cells at column 22, lines 10-34, and breast carcinoma cells at column 23, lines 16-43), Example VII **also** shows that sFN had **no** effect on two other established tumor types (C8161 melanoma and KR1B osteosarcoma cells at column 22, lines 35-38). If, as alleged in the statement, sFN as used in Example VII induces apoptosis of endothelial cells during angiogenesis in conjunction with an established tumor, then why was there no effect on two of the four established tumors tested? Clearly, this inconsistency demonstrates that Example VII simply does not support the notion that sFN inhibits angiogenesis, much less the notion that sFN induces apoptosis of endothelial cells. At best, Example VII appears to reflect some other effect of sFN, perhaps mediated by non-specific binding to receptors found on two of the tumor cell lines tested. The ambiguity in how sFN produces the results in Example VII directly contradicts the allegation on pages 6-7 of the Office Action. Accordingly, Pasqualini et al. (USP '676) does **not** disclose sFN as causing regression of all tumors.

Applicant respectfully points out, as noted in previous Responses and as set forth at M.P.E.P. §§ 2112, 2112.02, and the cases cited therein, that a case of inherency includes the requirement for "rationale or evidence tending to show inherency". As explained above, the rationale of sFN binding $\alpha 5\beta 1$ integrin and so anticipating the claims is insufficient given the ample evidence that sFN does not act as an $\alpha 5\beta 1$ integrin antagonist.

Moreover, and as explained previously, a case of inherency is only present if the alleged inherent feature is an inevitable outcome of a disclosure. In the instant case, there is no evidence from the cited references that sFN inevitably acts as an $\alpha 5\beta 1$ integrin antagonist.

Therefore, Applicant respectfully submits that no *prima facie* case of anticipation, based on inherency or otherwise, is present and that the instant rejection may be properly withdrawn.

Stated differently, and with particular respect to *In re Best* and the need for anticipation by inherency to prevent the improper patenting of old subject matter, Applicant points out that the instant claims do not attempt to patent an old process based on the discovery of a new property. Instead the claims are directed to new methods relying on the use of $\alpha 5\beta 1$ integrin antagonists that do not include sFN. The claims thus encompass patentable processes in

accordance with the standard set forth by M.P.E.P. §§ 2112 and 2112.02 and the cases cited therein. Accordingly, the rejection should be withdrawn and the rejected claims indicated as allowable over the cited references.

Rejection under 35 USC 103

Claims 121, 131-134, 145-146, and 148 were rejected under 35 § U.S.C. 103(a) as allegedly obvious over Pasqualini et al. (USP '676) as evidenced by PCT Application WO 95/14714 (Ruoslahti), Thorpe (Monoclonal Antibodies in Biological and Clinical Applications, Pinchera et al. eds, 475-506 (1985)), Guo et al. (Cancer Res., 57:1735-1742, 1997), and Scott et al. (J. Invest. Derm., 108:147-153, 1997). Applicant respectfully traverses the rejection as having failed to present a *prima facie* case of obviousness. As an initial matter, Applicant understands the inclusion of Thorpe as solely related to the use of cytotoxin conjugated antagonists.

The instant rejection is apparently based on the view that it would have been obvious to substitute peptides of WO 95/14714 for the sFN of Pasqualini et al. (USP '676) to inhibit cancer cell metastasis according to Example IX of Pasqualini et al. (USP '676) and as shown in Figures 5 and 6 of WO 95/14714. A review of Figures 5 and 6, as well as the discussion on page 5, lines 22-25, shows that they describe the use of various peptides to inhibit attachment of tumor cells to fibronectin. There is no disclosure or suggestion, however, that the binding of these peptides to **tumor** cells results in the inhibition of angiogenesis, much less induction of apoptosis in **endothelial** cells as encompassed by the present claims. The same is seen in a review of Example IX (as well as Figure 8B and column 27, lines 28-57) of Pasqualini et al. (USP '676), which also describes the use of sFN and peptides that apparently inhibit attachment of **tumor** cells to mouse lung tissue with a result of decreased lung weights. There is no disclosure or suggestion of inducing **endothelial** cell apoptosis by contacting **tumor** cells with peptides as disclosed by Pasqualini et al. (USP '676) and WO 95/14714.

There is also no disclosure or suggestion that the peptides of Pasqualini et al. (USP '676) or WO 95/14714 are $\alpha 5\beta 1$ integrin antagonists that induce apoptosis in endothelial cells. This deficiency is not remedied by combination of these references with Guo et al. and/or Scott et al.

Guo et al. state that growth of endothelial cells on a fibronectin substrate suppressed induction of apoptosis **mediated by TSP1 or certain peptides thereof** (see abstract). Because TSP1 and the peptides thereof are distinct from the peptides of Pasqualini et al. (USP '676) or WO 95/14714, Applicants respectfully submit that Guo et al. provides no information as to how the peptides of Pasqualini et al. (USP '676) and WO 95/14714 may or may not function on endothelial cells. Additionally, Guo et al. fail to teach or suggest that the induced apoptosis was due to TSP1, or the peptides thereof, acting as $\alpha5\beta1$ integrin antagonists or even by binding $\alpha5\beta1$ integrin. The asserted link between Guo et al. and Pasqualini et al. (USP '676) and WO 95/14714 appears to be the references to fibronectin. But as previously noted by Applicant and as disclosed in WO 95/14714 on page 2, lines 10-13, fibronectin binds many other receptors, including $\alpha v\beta3$, $\alpha v\beta5$, and $\alpha IIb\beta3$. Stated differently, while $\alpha5\beta1$ integrin might be specific for fibronectin, fibronectin is clearly not specific for $\alpha5\beta1$ integrin. Therefore Guo et al.'s observations on TSP1 and the peptides thereof may be due to their binding to other integrins as antagonists. This is consistent with the observation that TSP1 is a ligand for $\alpha v\beta3$ (see Guo et al., page 1741, left column, second full paragraph). Accordingly, it is unclear how the observations using Guo et al.'s TSP1 or TSP1 peptides provide any support for the assertion that the peptides of Pasqualini et al. (USP '676) or WO 95/14714 inhibit angiogenesis or induce apoptosis of endothelial cells by acting as an $\alpha5\beta1$ integrin antagonist.

Scott et al. describe the use of antibodies against the $\beta1$ integrin to enhance apoptosis of **melanocytes** attached to fibronectin. Because melanocytes are distinct from the cells of Pasqualini et al. (USP '676) and WO 95/14714, Applicants respectfully submit that Scott et al. provides no information on the effect of antibodies against $\beta1$ integrin in the tumor cells of Pasqualini et al. (USP '676) or WO 95/14714. Applicants thus respectfully urge that the observations of Scott et al. regarding melanocytes fail to support the assertion that the peptides of Pasqualini et al. (USP '676) or WO 95/14714 inhibit angiogenesis or induce apoptosis of endothelial cells by acting as an $\alpha5\beta1$ integrin antagonist.

Additionally, there is a lack of evidence that the antibodies used by Scott et al. bind $\beta1$ integrin in the context of an $\alpha5\beta1$ complex. As mentioned above and stated by Scott et al., "melanocyte attachment to FN [fibronectin] is mediated by multiple integrin receptors" (see page

151, right column, 15 and 16 lines from the bottom). Accordingly, Scott et al.'s observed effects in **melanocytes** may simply be the result of binding to integrin receptors other than $\alpha5\beta1$.

Moreover, the asserted link between the two pairs of references (Scott et al. with Guo et al. and Pasqualini et al. (USP '676) with WO 95/14714) appears to be the alleged involvement of fibronectin. But given the lack of specificity of fibronectin for $\alpha5\beta1$ integrin as noted above, the combination of Scott et al. and/or Guo et al. with Pasqualini et al. (USP '676) and WO 95/14714 lacks a nexus linking these two disparate pairs of references.

Applicant further notes that Scott et al. would actually lead an artisan of ordinary skill away from the instant claims. Scott et al. state "that $\alpha5\beta1$ receptor occupancy [by fibronectin] alone is insufficient for full suppression of apoptosis" (see page 151, right column, 13 and 14 lines from the bottom). Stated differently, Scott et al. teach that other receptors to ECM interactions contribute to the suppression of apoptosis, and so there could be no reasonable expectation that an $\alpha5\beta1$ integrin antagonist **alone**, as presently claimed, would successfully induce apoptosis or inhibit angiogenesis.

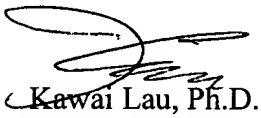
In view of the foregoing arguments, Applicant respectfully submits that no combination of Pasqualini et al. (USP '676), WO 95/14714 (Ruoslahti), Guo et al., and Scott et al. is sufficient to support a *prima facie* case of obviousness against the instant claims. Additionally, the combination of the first two references with the latter two lacks a logical nexus. Moreover, Thorpe fails to remedy the above noted deficiencies or address the absence of an expectation of success in the instant rejection. Accordingly, Applicant respectfully submits that no case of obviousness is present, and that the instant rejection should be withdrawn.

CONCLUSION

In view of the foregoing, Applicant believes that all claims now pending in this Application are in condition for allowance and urge early indication to that effect.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6108 in San Diego, but use the San Francisco address for written correspondence.

Respectfully submitted,



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